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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
10/696,389	10-29-03	BONI	TRA-00801

EXAMINER
KISHORE

ART UNIT	PAPER NUMBER
1615	

DATE MAILED:

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) G S KISHORE (3) Dr. WALTER PERKINS

(2) Dr. HILARY LANG (4) _____

Date of Interview 11-19-07

Type: ☐ Telephonic ☐ Televideo Conference ☐ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or ~~demonstration~~ conducted: ☒ Yes ☐ No If yes, brief description: _____

Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: claims on record

Identification of prior art discussed: —

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Dr Perkins explained the higher amounts of encapsulation of amikacin once using an ethanol injection method used in instantly claimed treatment method. Since the claims are drawn to a method of treatment, the following were suggested 1) limit to aminoglycoside or amikacin, 2) recite specific components of liposomes & drug amounts 3) introduce cystic fibrosis 4) RCE will be filed and the allowability of the claims will be determined after further search.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

Examiner Note: You must sign this form unless it is an attachment to another form.

G S Kishore

Gollamudi S. Kishore, PhD
Primary Examiner
Group 1600

FORM PTOL-413 (REV. 2-98)

Manual of Patent Examining Procedure, Section 713.04 Substance of Interview must Be Made of Record

Except as otherwise provided, a complete written statement as to the substance of any face-to-face or telephone interview with regard to an application must be made of record in the application, whether or not an agreement with the examiner was reached at the interview.

§1.133 Interviews

* * * * *

(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111 and 1.135. (35 U.S.C. 132)

§ 1.2. Business to be transacted in writing. All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf Interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, pointing out typographical errors or unreadable script in Office actions or the like, or resulting in an examiner's amendment that fully sets forth the agreement are excluded from the interview recordation procedures below.

The Interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and listed on the "Contents" list on the file wrapper. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication.

The Form provides for recordation of the following information:

- Application Number of the application
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (personal or telephonic)
- Name of participant(s)) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desireable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check a box at the bottom of the Form informing the applicant that he need not supplement the Form by submitting a separate record of the substance of the interview.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview:

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner,
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter to complete the reply and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the statement attributed to him. If the record is complete and accurate, the examiner should place the indication "Interview record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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Inhalation Biotherapeutics

Patent Office Visit
November 19, 2007

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Process to Entrap Amikacin

Amikacin Liposomes by EtOH Addition

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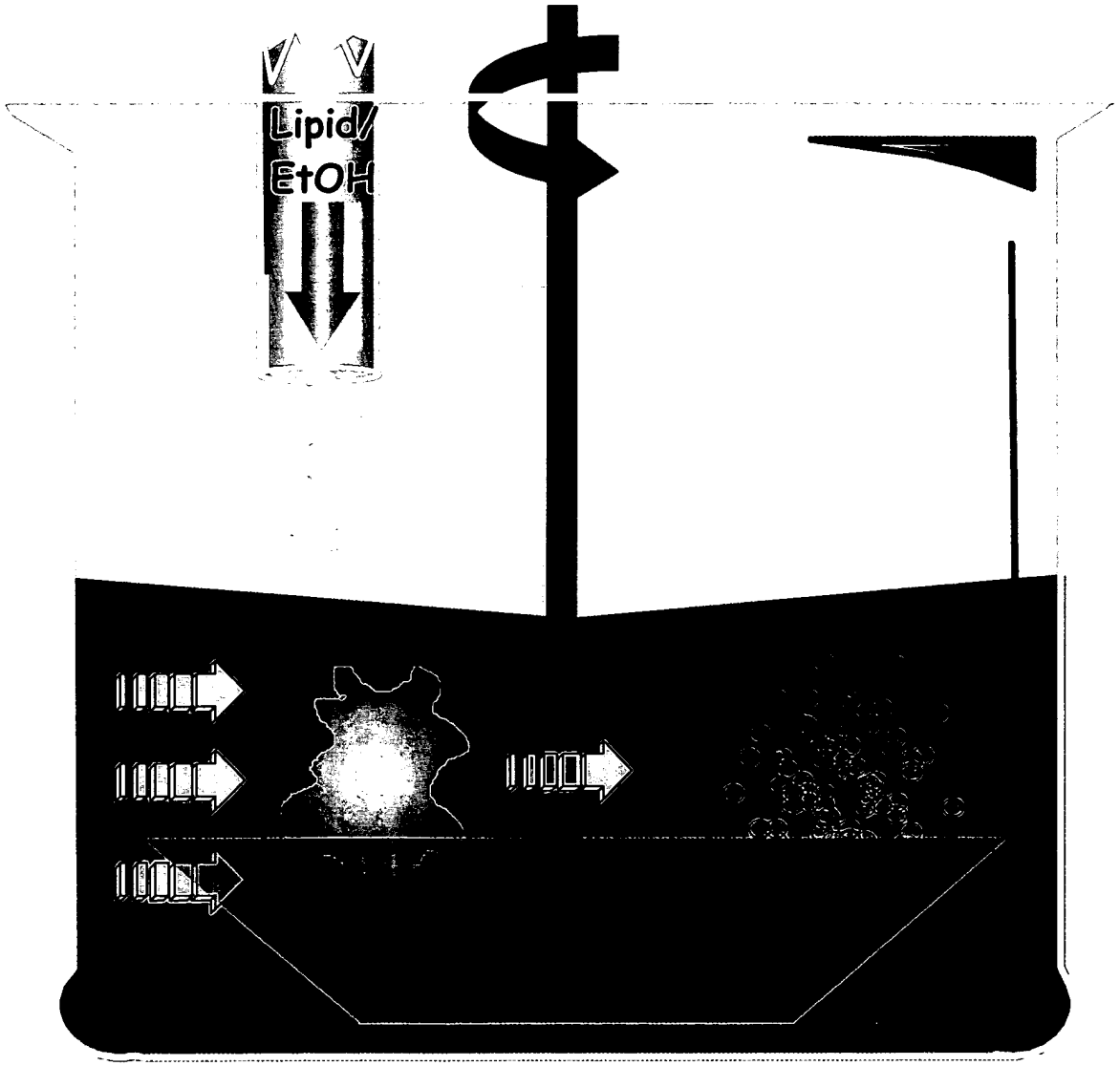

Ethanol Infusion Process (with Addition from Above Solution Surface) Resulted in Unexpected Entrapment Levels

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Table 6. Amikacin loading into liposomes prepared by different methods.

Measured Parameter	Sample #			
	1	2	3	4
Lipids concentration (mg/ml)	35.1	39.5	50.4	45.0
AMK concentration (mg/ml)	19.9	20.7	10.5	5.0
Actual Lipid/Drug (w/w)	**1.8**	**1.9**	**4.8**	**9.0**
Entrapped volume (µl/µmole)	**2.4**	**2.5**	**2.9**	**1.6**
Expected Lipid/Drug (w/w)	**5.6**	**6.0**	**4.1**	**8.1**
Expected / Actual L/D ratio	**3.19**	**3.17**	**0.85**	**0.90**
Liposome Size (µm)	0.230	0.217	4.65	3.96

Samples 1 and 2 were made by the ethanol infusion procedure disclosed herein, and Samples 3 and 4 were made by liposome formation techniques known in the art.

Taken From Filed Application

EtOH Injection into Solution

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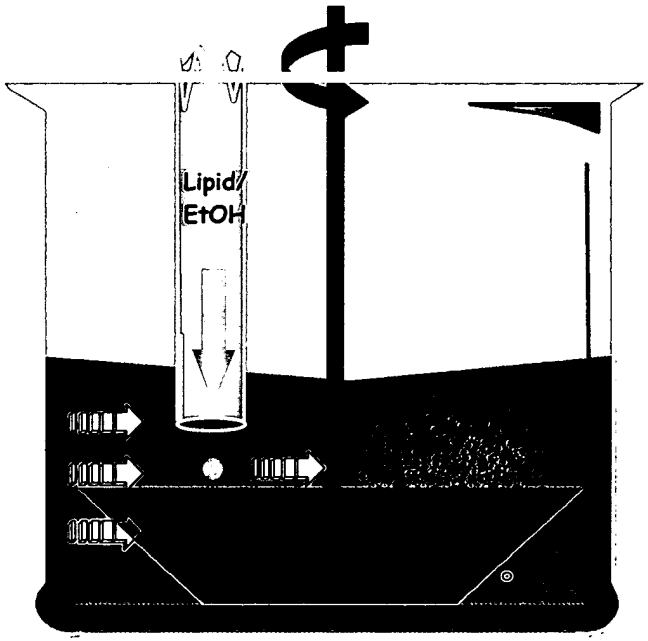
Lower entrapment if :

- **Inject directly into solution rather than from above**

- **Add EtOH at 50°C as opposed to room temp (5X lower)**



Faster Infusion Rate of Lipid-Ethanol Solution to Aqueous Phase Leads to More Efficient Entrapment

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Batch #	R-1	R-2	R-3	R-4	R6
Infusion Rate (ml/min)	4.7	23	63	300	1000
Lipids (mg/ml)	49.6	49	46.8	39.5	36.5
Entrapped volume (µl/µlmole)	0.80	0.82	1.38	1.67	nd
Actual AMK conc (mg/ml)	9.1	10.9	12.6	20.9	20.4
Actual/Expected ratio	**2.77**	**3.26**	**2.37**	**3.82**	**--**
Lipid/Drug (w/w)	5.43	4.51	3.71	1.89	1.79

Faster Infusion Rate of Lipid-Ethanol Solution to Aqueous Phase Leads to More Efficient Entrapment

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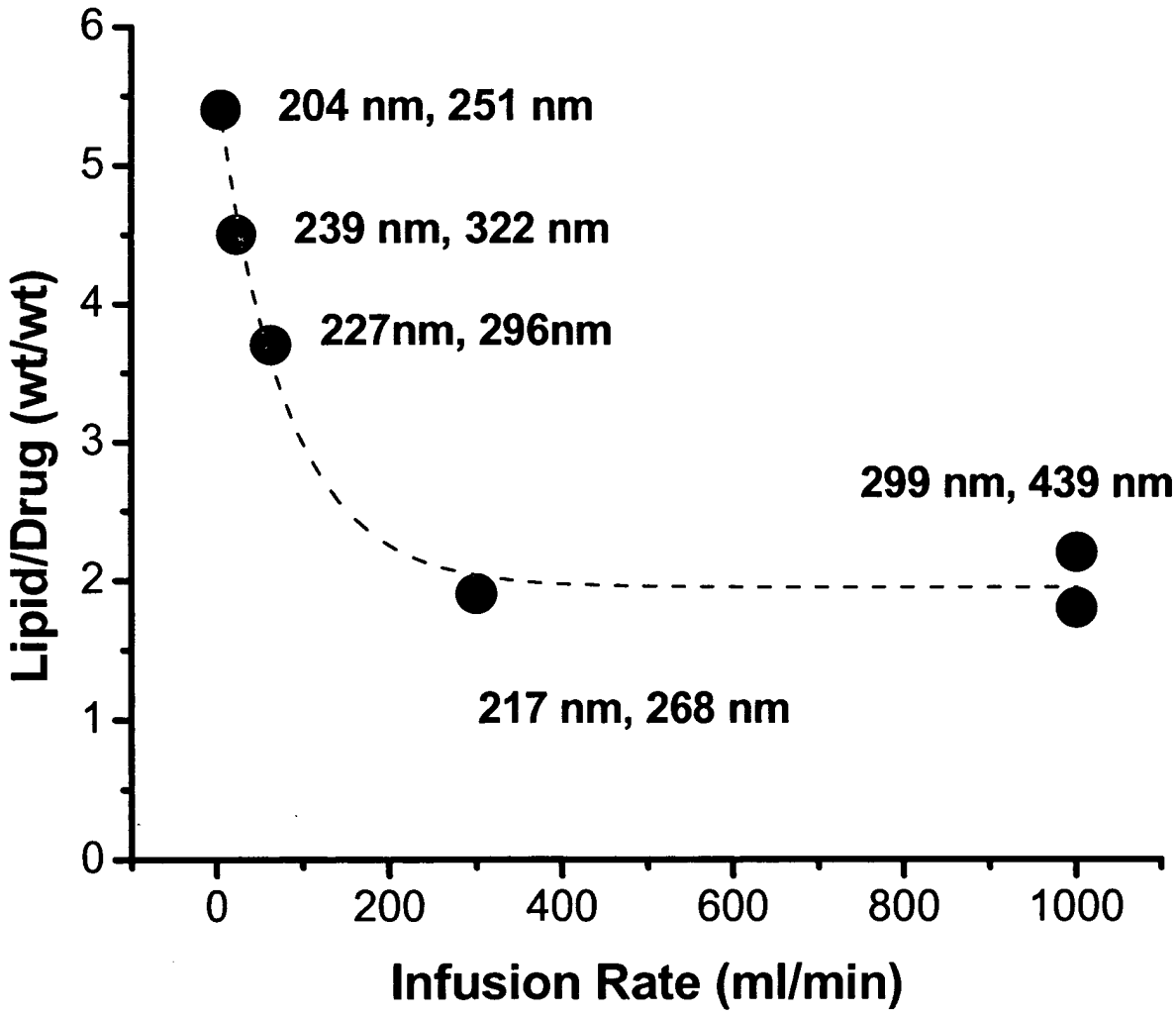

Key to Success: Liposome Entrapment Exceeds Theory via Coacervation

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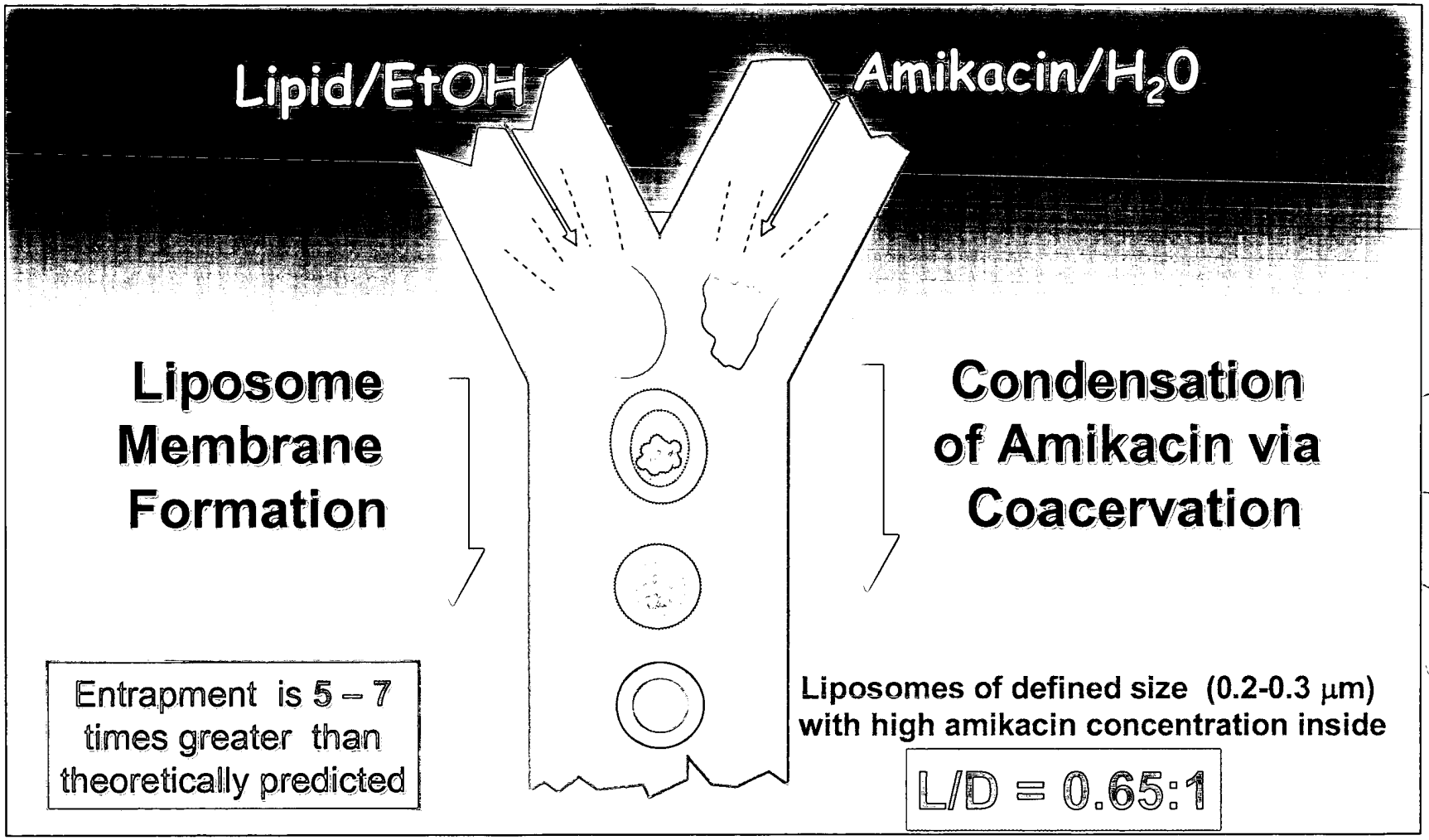

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Liposomal Amikacin given Once Daily is Superior to Amikacin or Tobramycin Given Once Daily

Free drug was ineffective at same dose and still not as good as liposomal at 10 x greater dose

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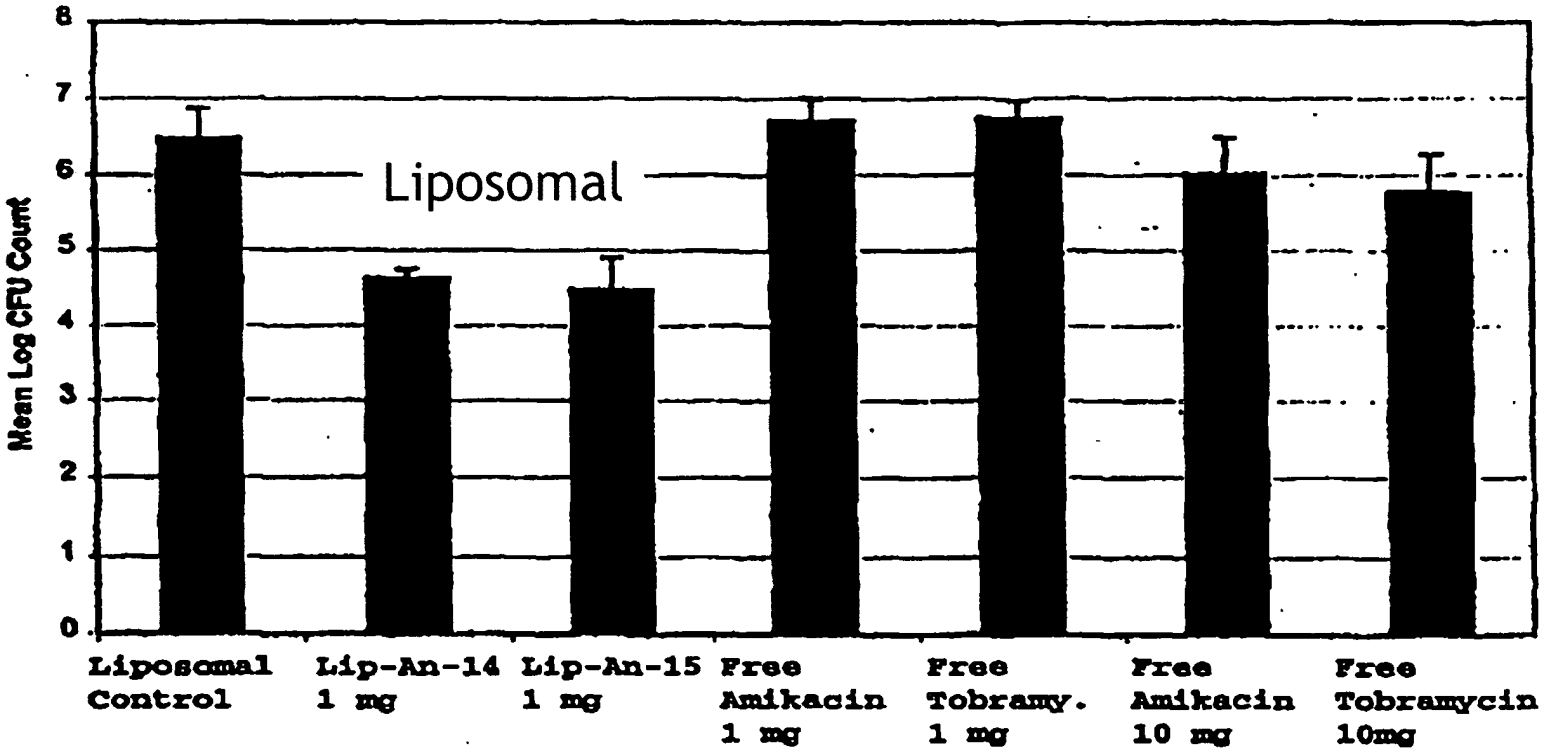
Therapy given every other day for 14 days

Figure 4



Taken From Filed Application

Once-a-Day Arikace™ Is as Efficacious as Twice Daily Tobramycin in P. aeruginosa Model (Woods)

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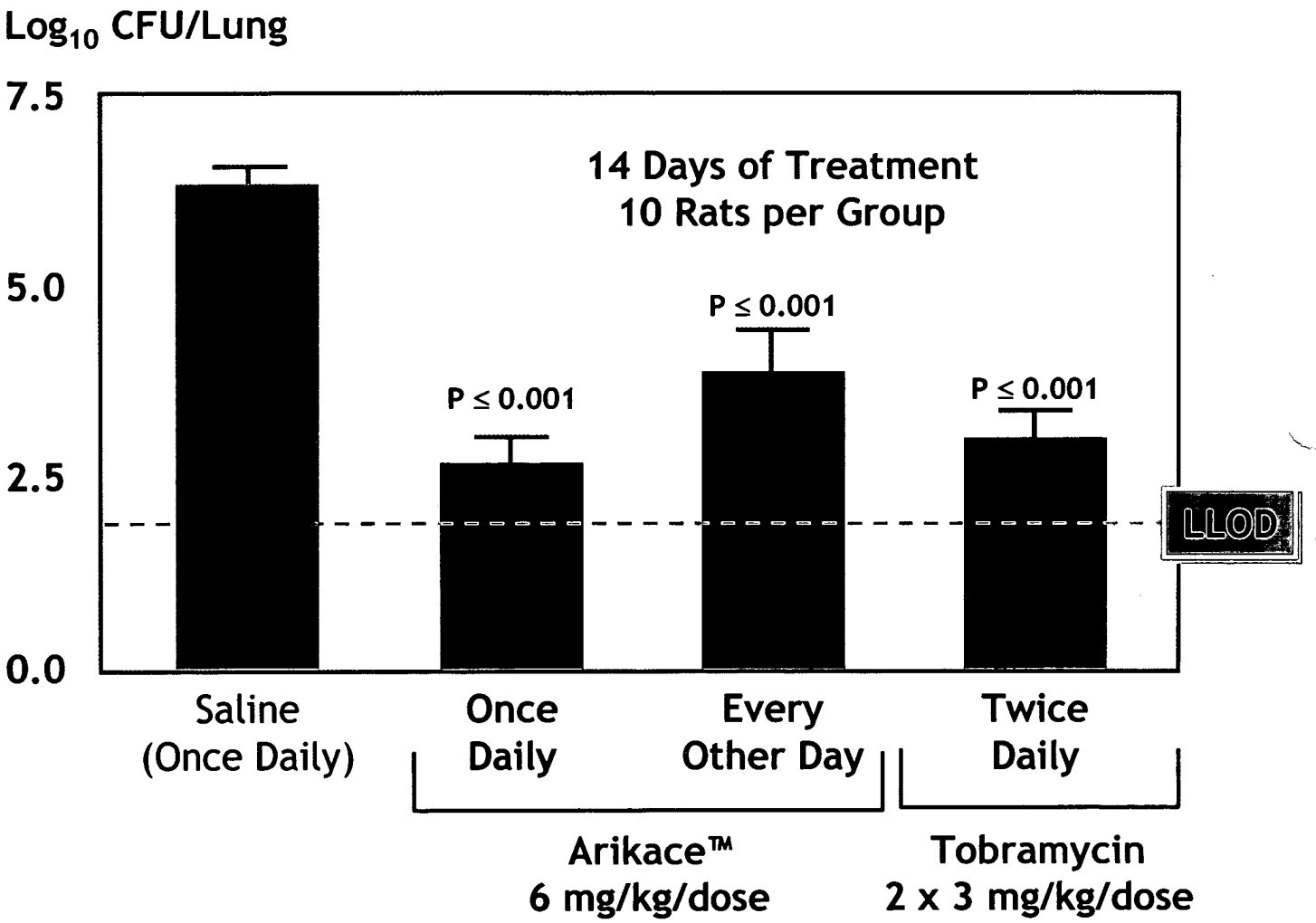

Half-life of Liposomal Amikacin is in Days
Half-life of Tobramycin is <2 hours

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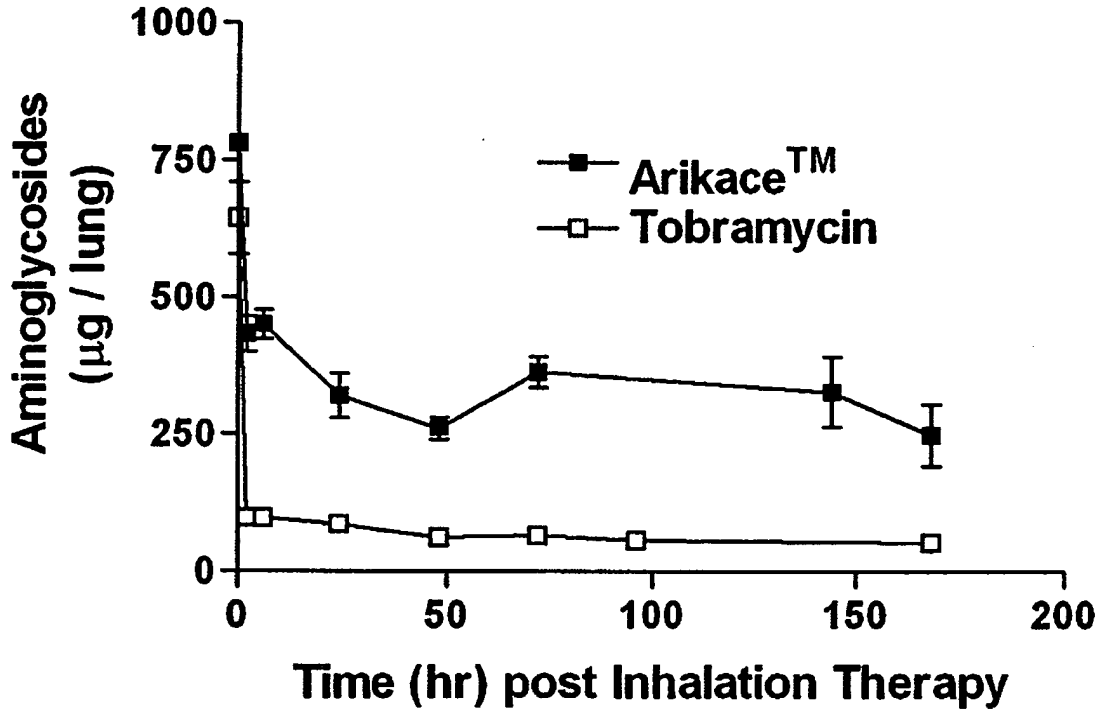

Figure 1. Rat Lung Pharmacokinetics of Arikace™ and Free Tobramycin post inhalation. Arikace™ 75mg/mL was administered by nebulization for 80 min. and tobramycin (60mg/ml) was administered for 100 minutes. The symbols and bars represent the mean and standard deviation of mean concentrations of aminoglycoside in the lung (n=2, 0 hr; n=3, 2-168 hr) at each sampling time.

Arikace™: The Only Once per Day Inhaled Antibiotic

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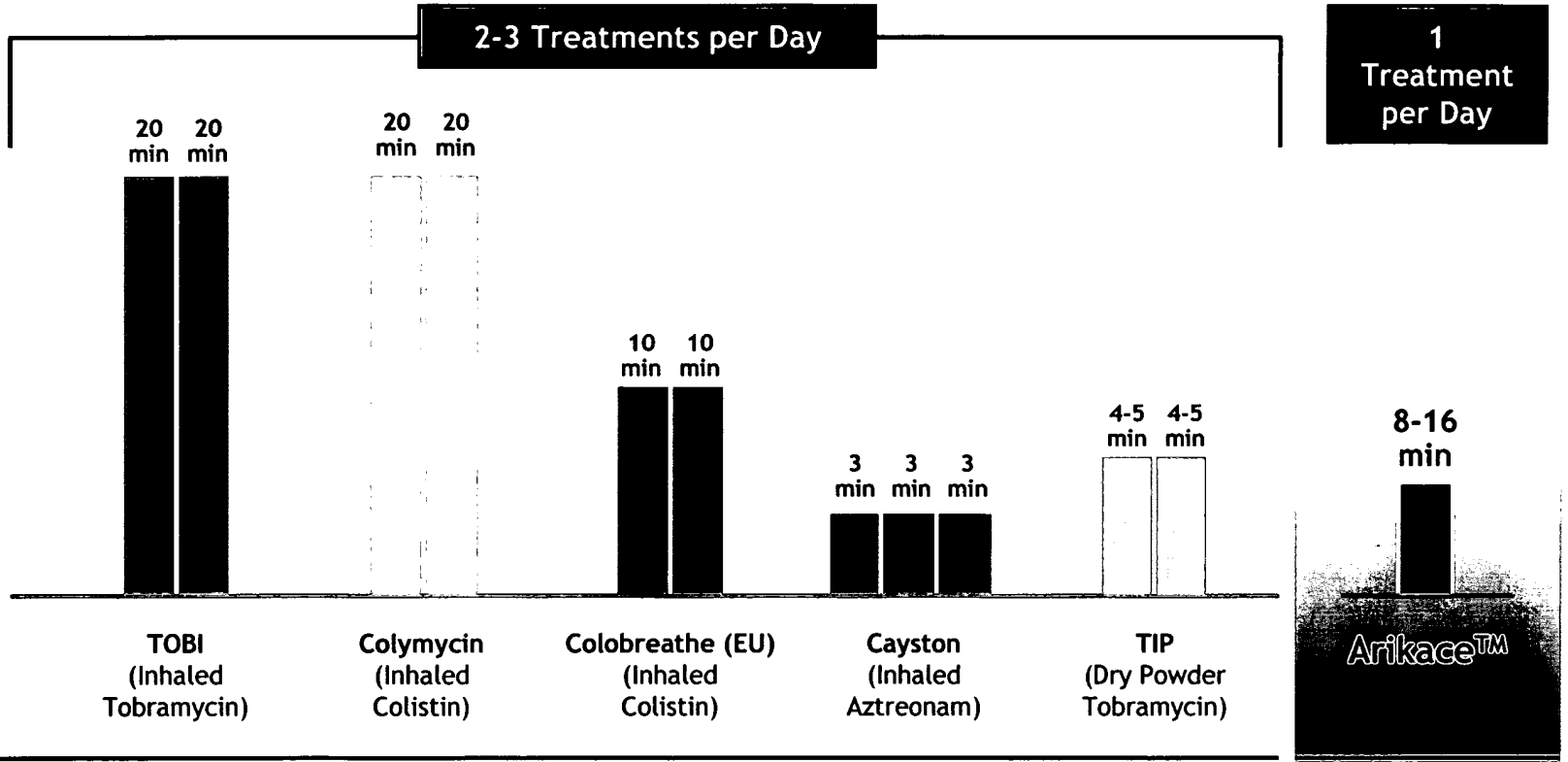
Treatment Comparison



	TOBI (Inhaled Tobramycin)	Colymycin (Inhaled Colistin)	Colobreathe (EU) (Inhaled Colistin)	Cayston (Inhaled Aztreonam)	TIP (Dry Powder Tobramycin)	Arikace™
Total Treatment Minutes / Day	40	40	20	9-10	8-10	8-16
Availability	Today	Today	2008	2008	2009	2011

Time to administer liposomal amikacin is dependent on L/D

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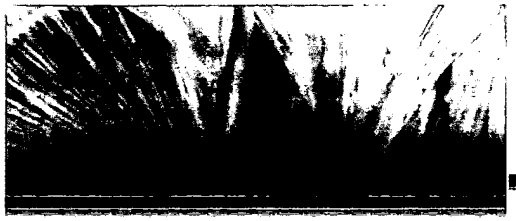
Lipid/Drug (W/W)	Upper End for lipid conc* (mg/ml)	Drug Concentration (mg/ml)	Nebulizer Output rate** (ml/min)	Time to Nebulize 300 mg dose (min)
10 : 1	50	5.0	0.5	120
4.0 : 1	50	12.5	0.5	48
3.5 : 1	50	14.3	0.5	42
3.0 : 1	50	16.7	0.5	36
2.5 : 1	50	20.0	0.5	30
2.0 : 1	50	25.0	0.5	24
1.5 : 1	50	33.3	0.5	18
1.0 : 1	50	50.0	0.5	12
0.65 : 1	50	77.0	0.5	8

*Viscosity limits of liposome solution limits upper end.

**Based on eFlow which is considered top nebulizer available for liposomes - see attached poster.



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AEROSOLIZATION OF LIPOSOMAL AMIKACIN (ARIKACE™) USING DIFFERENT NEBULIZERS: SELECTION OF THE eFLOW® NEBULIZER

Perkins, Walter R[1]; Li, Zhili[1]; Wenker, Andreas[2]; Mullinger, Bernhard[2]
[1]Transave, Inc., Monmouth Junction, NJ, USA; [2]Activaero, GmbH, Gauting, Germany

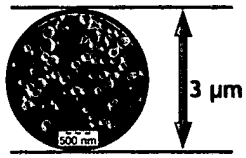
Poster Presented at NACF Meeting October 2007

Introduction

Arikace™ is an inhalation formulation of a liposomal amikacin suspension that is designed to treat chronic *Pseudomonas aeruginosa* infections in cystic fibrosis patients. Liposome encapsulation of amikacin 1) reduces non-specific binding of this cationic aminoglycoside drug to the negatively charged mucus and biofilm surfaces and 2) allows penetration and delivery of packets of highly concentrated drug to the otherwise protected bacteria within the biofilm. As nebulized and delivered to the lungs, Arikace™ comprises 65% liposomal amikacin and 35% 'free' amikacin that is not entrapped by liposomes; free drug is produced by liposome leakage during nebulization. This profile provides an initial high peak concentration of amikacin followed by a sustained level as drug leaks from the liposomes. Nebulized Arikace™ with this profile was evaluated previously in human clinical studies using the PARI LC STAR® nebulizer. The 0.3 µm liposomes of Arikace™ are efficiently loaded with drug (lipid/drug = 0.7 w/w) and the liposome concentration is near a maximum value for nebulization (beyond this concentration viscosity reduces flow). With an optimized formulation, further improvement in reducing dose administration can only be achieved through selection of an efficient nebulizer.

Goal:

To minimize treatment time and improve patient convenience we sought to find a nebulizer that would efficiently deposit Arikace™ and produce aerosol at a high output rate, while still producing the same level of free drug (35%) during nebulization.



~ 300 liposomes in 3 micron droplet

Figure 1. Freeze-fracture electron micrograph of Arikace™. Liposomes are typically 0.2-0.3 µm in diameter. The image is shown relative to the cross-sectional area of an aqueous droplet 3 µm in diameter.

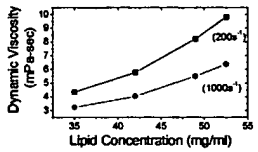


Figure 2. Dynamic viscosity of Arikace™ as a function of lipid concentration.

Methods

Nebulization of liposomal amikacin was compared using several nebulizers, including 2 jet nebulizers: LC STAR® and LC SPRINT® (both by PARI), and 3 electronic mesh nebulizers: MicroAir® NE U22V (Omron), AeronebGo® (Nektar), and eFlow® (PARI); the ultrasonic nebulizer Multisonic® (Schill) was also evaluated. All nebulizers are trademarked products of the companies indicated. Additionally, meshes of different pore sizes were examined for the MicroAir® and eFlow® devices. Output rates were measured by gravimetric differences. Droplet size distribution was assessed by a laser light scattering method (Malvern Master SizerX V2.15) and by cascade impaction (Andersen Cascade Impactor); mass median aerodynamic diameters (MMAD), geometric standard deviation (GSD), and fine particle fraction (FPF) (i.e., % droplet mass <5 µm). Amikacin association with the liposomes was measured using a centrifugation-filtration assay where a Centricon and/or Centrisart device was used which allowed the physical separation of the outer aqueous solution from the liposomes. Assay of this fraction for amikacin and comparison to the amikacin concentration in the whole sample allowed % free and associated to be calculated. Dynamic viscosity was measured using a Rheo Stress 1 instrument (Haake); the dynamic viscosity for Arikace™ (70 mg/ml) is 8.2 mPa·sec (200 s-1) and 5.5 mPa·sec (1000 s-1).

Note: Testing of the eFlow® device with Arikace™ was conducted at PARI Pharma Labs, Munich, Germany.

Results

Table 1. Output Rates of Nebulizers with Arikace™

Nebulizer	Type	Reported Deposition* (% based on fill)	Amikacin (mg/ml)	Output rate	
				gram/min	mg Amik/min
LC STAR®	Jet	16	75	0.18 - 0.27***	13.5-19.6
LC SPRINT®	Jet	--	75	0.32 - 0.43***	23.9 – 31.9
Multisonic®	Ultra-sonic	39**	30	0.19	5.70
			75	0	0
AeronebGo®	Mesh	24	45	0.33	14.7
			58	0.33	18.9
			60	0.17	10.0
MicroAir®	Mesh (3µm)	--	15	0.33	5.0
			75	0	0
	Mesh (6µm)	35	47	0.29	13.4
			58	0	0
eFlow®	Mesh (40L)	30	48	0.51	24.5
			72	0.44	31.7
	Mesh (45L)	--	48	0.76	36.5
			72	0.61	44.0
	Mesh (50L)	--	48	0.88	42.0
			72	0.67	48.0

*Deposition factor for the LC STAR® based on a scintigraphic study (16%) with liposomal amikacin 20 mg/mL (*Weers et al., 2005*) and published scintigraphy data (15%) for the LC STAR® (*Finley et al., 1998*). Deposition factors for mesh nebulizers are 35% for MicroAir® NE-U22V, 24% for AeronebGo® (*Vecellio et al., 2006*). **Percent of emitted dose deposited, (*Kohler et al., 2003*). ***Devilbiss Compressor operated at 30 psi.

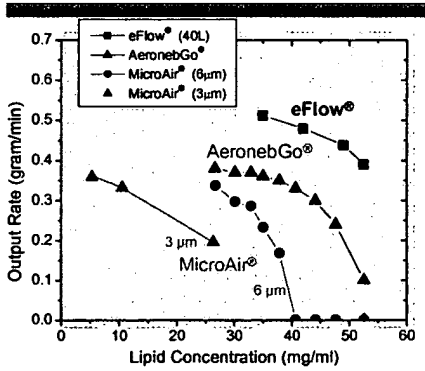


Figure 3. Output rates of various mesh nebulizers as a function of Arikace™ (i.e., lipid) concentration. For the PARI eFlow®, the 40L mesh was examined. For the Omron MicroAir® a 3 and 6 µm mesh was examined. The AeronebGo® was used as purchased with its standard mesh.

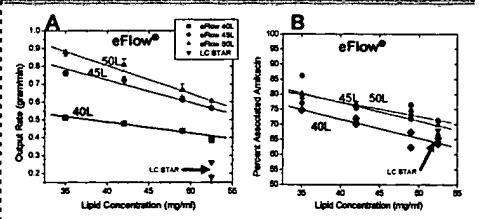


Figure 4. A) Aerosol output rate and B) percent associated amikacin as a function of Arikace™ (i.e., lipid) concentration for various nebulizer configurations. eFlow® units with meshes of differing size (40L (black diamonds), 45L (red circles) and 50L (green triangles)) and the PARI LC STAR® were evaluated (blue inverted triangles). Error bars = SD. Lines are linear regression fits of data.

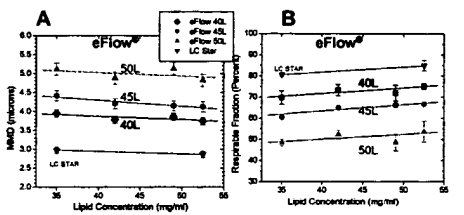


Figure 5. A) Aerosol droplet diameter as measured by laser diffraction (mass median diameter, MMD) and B) the derived respirable fraction (%<5 microns) as a function of Arikace™ (i.e., lipid) concentration for various nebulizer configurations. Various meshes were examined with the eFlow®; symbols are the same as those defined in the Figure 4 legend. Error bars = SD. Lines are linear regression fits of data.

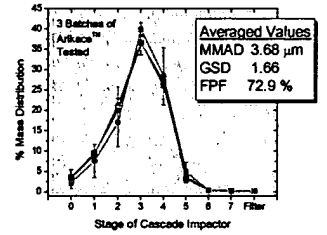


Figure 6. Distribution of Arikace™ on various stages of an Andersen Cascade Impactor (ACI). Nebulization was performed with the eFlow® 40L device. Conditions: 18°C, 50% RH, 28.3 L/min flow. Three batches of Arikace™ were tested. FPF= (% < 5µm). Error bars = SD, (n=3 measurements per batch).

Conclusions

- **Arikace™ nebulization was evaluated in multiple devices including jet, ultrasonic, and electronic-mesh nebulizers**
- **In terms of nebulizer output rate (mg amikacin/minute) the order was eFlow® > LC SPRINT® > AeronebGo® ≈ LC STAR® > MicroAir® > Multisonic®**
- **Arikace™ nebulized via the eFLow® 40L device exhibited an acceptable amount of amikacin release at 30-35% and with an appropriate droplet size (MMAD = 3.7µm and FPF ~73%) for efficient lung deposition**